REMARKS

In response to the Official Action in which prosecution was reopened in accordance with the Order dated January 20, 2000, applicant hereby elects to file a reply pursuant to the provisions of 37 C.F.R. §1.193(b)(2)(i). The instant response, makes a minor correction of an obvious typographical error in the specification, but does not amend the claims since applicant firmly believes that the presently claimed invention is patentable over the cited prior art, including the new documents cited in the Action, and is also patentable over the claims of the cited commonly assigned patents.

Before addressing each of the grounds set forth in the Action, applicant believes that a discussion of the background and important aspects of the present invention is in order. The present invention relates to a method and device for administering fentanyl by iontophoresis. Fentanyl is prescribed for treating post-operative pain and is a potent narcotic which is about 80 times stronger than morphine. Irrespective of the nature of delivery, due to its opiate character and strength, fentanyl has the potential of being abused as demonstrated by the evidence that has been made of record. This potential is so well recognized that the Merck Index includes the statement: "Caution: Abuse leads to habituation or addiction."[1] With the documented current misuse of another prescription narcotic, Oxycontin, it is clear that the potential for fentanyl abuse is a real concern.

In designing delivery systems for drugs such as fentanyl, those skilled in the art would logically seek to provide a system that is essentially void of drug at the conclusion

[1] Excerpt from the Tenth Edition of the Merck Index is attached.

of the designed administration period. Just as one would not discard a syringe with residual morphine in the reservoir, one would seek to avoid a device which contains residual fentanyl when the administration period has concluded. Why not

The design of an iontophoretic device for administering fentanyl would at first blush seem to be straightforward. One would calculate the total amount of fentanyl to be delivered over the administration period and add that amount to the reservoir. One would expect that the iontophoretic flux would be determined by the current, not the concentration of the drug in the reservoir. Such expectation would be based on experience with drugs of similar molecular weight, such as hydromorphone, that is reported in the article of record by R. V. Padmanabhan et al entitled "*In Vitro* and *In Vivo* Evaluation of Transdermal Iontophoretic Delivery of Hydromorphone" which states on page 130:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

Against this background, applicant has found quite unexpectedly that the concentration of fentanyl salt in the donor reservoir must be above the unexpectedly high level of about 16 mM substantially throughout the total delivery period in order to avoid having the iontophoretic flux being dependent on the concentration of the fentanyl salt. This finding is illustrated by Figure 2 of the present application and is contrary to what one would expect. In fact, the experiments described in the Padmanabhan article include instances wherein the **starting** concentration is 0.01M or 10 mM which is below the

ending concentration in accordance with the present invention. In other words, contrary to what would be expected, applicant has found that one must maintain the concentration of fentanyl salt above about 16 mM substantially throughout the total delivery period in order to avoid a substantial change in the iontophoretic flux.

The claimed high concentration of fentanyl salt is a particular characteristic of the compound itself and is not due to the presence of any competing ions. Thus, as can be determined from Example 1, the only competing cations are from the 0.5 N sodium hydroxide. However, there are approximately seven times the amount of fentanyl cations originally present in the reservoir. Moreover, as the iontophoretic delivery progresses, the sodium ions, being smaller and more mobile, will be transported more quickly as delivery progresses so that there are substantially no sodium ions remaining in the reservoir to "compete" with the fentanyl ions. This is precisely what Dr. Phipps explained in his Declaration Under 37 C.F.R. § 1.132 that was filed on August 3, 1998.

The discussion at the bottom of page 25 of the application does not contradict this understanding. The statement that as the fentanyl HCl concentration falls below 6 mg/ml (about 16 mM), a more significant portion of the electrotransport current is carried by ions other than fentanyl ions refers to the increasing effect of chloride ions which migrate from the other side of the epidermis. It has nothing to do with ions originally present in the donor reservoir. Thus, the reference to the effect of "competing" ions, such as potassium, in the art relied on by the Examiner actually further supports the patentability of the

present invention since the claimed high fentanyl salt concentration is again a function of the compound itself and not due to the presence of "competing" ions.

Based on the foregoing discussion and with a complete understanding of the invention as developed during the extensive prosecution history of the present application, those of ordinary skill in the art will recognize that the presently claimed invention is patentable over the various combinations of documents set forth in the Official Action. In particular, the Examiner has first attempted to reject all of the claims over the combined teachings of Phipps et al., U.S. Patent No. 5,423,739, in view of the translation from a Russian document referred to as Rebinder, and further combined with Phipps et al., U.S. Patent No. 5,125,894, and Mueller et al., U.S. Patent No. 5,320,731.

The '739 patent discloses an iontophoretic device having a two-layer active electrode element which is composed of an overlapping skin contact hydrogel and carrier layers with the carrier layer containing dispersed or dissolved active agent. In describing the administration of the agent, the '739 patent states at column 9, lines 27-34:

> The agent can be dispersed or dissolved, alternatively in neutral form, or in salt or ionic form if stable, and in high concentration in the carrier of the two layer element or in the polymer of the single layer or in the hydrating medium for the single layer. Upon combination, the rate of transport can be controlled by the current so as to provide a sustained therapeutic level of the active agent.

The active agents which can be administered by the disclosed device are set forth in the extensive list which encompasses columns 13 and 14 and includes fentanyl, but only hydromorphone and lidocaine are exemplified.

Apparently concerned with the failure of the '739 patent to specifically address the administration of fentanyl, the Examiner has attempted to rely on two additional patents, namely Theeuwes et al., U.S. Patent No. 5,232,438, and Petelenz et al., U.S. Patent No. 4,752,285, (thereby resulting in an actual combination of six documents in the rejection) to show the electro transport of fentanyl salts and the use of hydrogels.

Even if these additional patents can be properly incorporated into the rejection, there were certain teachings therein which confirm the points provided above. For instance, in Theeuwes et al., the patent describes a ratio of electrokinetic flux to passive flux and states at column 7, lines 44-45 that a mathematical equation "indicates that it may be advantageous to operate at a low donor drug concentration." Moreover, the patent states at column 15, lines 19-21 that the relationship between steady state electrically-assisted transport, the defined ratio and the current density were found to be linear. As to Petelenz et al., the very passage cited by the Examiner at column 16, line 45-58 includes the caveat of the possibility of narcotics being improperly extracted from the electrode of an iontophoretic device and misused. Thus, these additional patents cited by the Examiner support the points raised above and the patentability of the present invention.

After acknowledging that the '739 patent fails to specify the particulars of the claimed invention, the Examiner has then boldly concluded on page 4 of the Action that the claimed concentration "would have been obvious to anyone of any skill in the art who had read the Phipps's '739 disclosure." Such conclusion is blatantly incorrect. Aside from the aforementioned portion of the '739 patent which states that the rate of transport can be

controlled by the current, the unsupported conclusion ignores the aforementioned teaching set forth in the Padmanabhan article which explicitly concludes that the iontophoretic delivery was found to be independent of the concentration in the donor solution. Since the article relates to the delivery of hydromorphone, which is the drug used in all but one of the Examples of the '739 patent, it is without question that such concrete evidence cannot be ignored compared to the Examiner's unsupported conclusion of obviousness.

The newly cited translation of Rebinder falls far short from being sufficient to justify a rejection of the claims even if properly considered with the other documents of record. Rebinder is a general description of iontophoresis, but does not specifically relate to the iontophoretic delivery of fentanyl which is different from other drugs for the reasons previously provided. Rebinder provides certain observations based on limited studies that had been conducted up to 1956 (the apparent date of the document cited by the Examiner). While the Examiner has referred to certain portions of the translation, on pages 6 and 7 of the Action, what has been omitted is the discussion under Section 45 starting on page 10 of the translation which is entitled "Fundamentals of Iontophoresis". In stating various principles, this portion of the article provides certain equations and explicitly states on page 12:

> It is important to note that the quantity n_1, and thus, in accordance with equation (253), the amount of substance introduced, is completely governed by the parameters of the internal solution and the skin tissue, and does not depend on the concentration of the medicinal substance used for iontophoresis.

Even the statements actually quoted by the Examiner do not support his conclusion when all of the evidence is considered. For instance, the passage quoted at the top of page 6 of the Action notes that with certain complex organic ions the higher the concentration of initial solution, the greater the therapeutic effect. The same passage recognizes, however, that for a number of simple ions, tenfold changes in the concentration have practically no effect on the amount introduced within the limits of experimental error. Such description in Rebinder would certainly not lead to an understanding of the present invention wherein the defined concentration of fentanyl salt has to be maintained substantially throughout the total delivery. All this passage states is that the **initial** concentration of the solution might have an effect. Moreover, when one considers the structure of hydromorphone (excerpt from the Merck Index also attached hereto) which is more complex than that of fentanyl and the aforementioned teachings in the art concerning the very low levels of hydromorphone concentration will maintaining constant flux, it can again be understood that the present invention is based on a surprising discovery.

As to the Examiner's citation to the discussion in Rebinder concerning "parasitic" ions, it has previously been explained that this phenomenon is not responsible for the present invention. Furthermore, the phenomenon observed in Rebinder is merely a comparison with the amount of dye delivered when no "parasitical" ions or a relatively low concentration of such ions are present. It does not teach that the concentration of the delivered material at the end of the delivery period must be maintained at a high level in order to maintain a relatively constant iontophoretic flux. In other words, this portion of

Rebinder simply indicates that if a large percentage of "parasitical" ions is initially present, the delivery of the other material in the reservoir will be less than if the "parasitical" ions are absent. Such observation has nothing to do with the present invention.

From the foregoing discussion, those of ordinary skill in the art will appreciate that the Examiner's four points set forth in the paragraph bridging pages 7 and 8 of the Action merely confirm that the prior art does not lead to the presently claimed invention. At best, the Examiner has simply postulated an "obvious to try" situation, which has consistently been found to be insufficient to establish obviousness.[2]

The '894 patent relates to a method and apparatus for conducting controlled environment electrotransport, particularly by controlling the ionic environment of the donor electro reservoir. The patent indicates that control can be achieved by maintaining the pH at a certain level or by maintaining selective control over the delivery rate of a target species. In the passage beginning at column 9, line 65, the '894 patent provides "Some General Observations Regarding Iontophoresis" and in this passage provides the statement:

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[2] Although the Examiner certainly has not contended that it is proper to apply an "obvious to try" standard, he has tried to analogize the results of the present application with those set forth in the cited Merck & Co. v. BioCraft Laboratories Inc., 10 USPQ2d 1843 (Fed. Cir. 1989) which applicant has previously cited during the prosecution of the present application. What is present in the instant situation relative to the fact situation in Merck is the significant teachings in the art of the linearity between current and concentration coupled with the very low threshold concentrations described in the art, particularly the aforementioned Padmanabhan article. Thus, while the legal principle set forth in Merck is applicable, the factual background is different.

> In general, the amount of transport which occurs as a result of applied voltage is directly proportional to the amount of current passing through the cell.

The '894 patent continues with the description of various factors that can effect electrotransport including the charge of the migrating species, the presence of extraneous ions in the active reservoir and the effect of the concentration of drug ions. With regard to this last factor, the patent refers to the aforementioned Padmanabhan article and states:

> In general, although rate of drug delivery is proportional to current, at a constant current the rate of drug delivery (R_d) is independent of drug concentration (i.e., target species concentration) in the active electrode reservoir, provided that the concentration is at least above a threshold level (and little or no extraneous ions are present) (citation to Padmanabhan omitted).

Based on this general statement, the Examiner has concluded that it would be obvious to determine the threshold level for fentanyl despite the fact that the '894 patent does not even mention fentanyl. Quite to the contrary, the '894 patent describes the iontophoretic delivery of hydromorphone and which shows in Table 2 that even with a drug concentration as low as 10 mM, the average steady state rate is approximately the same as it is at 800 mM. Moreover, in the passage bridging columns 34 and 35, the patent makes the observation that when extraneous ions are present, such as sodium and potassium, they are transported at a faster rate than the hydromorphone which is precisely what was discussed above to explain why extraneous ions are not responsible for the high concentration defined in the claims of record.

As for the Examiner's reliance on the threshold level mentioned in the '894 patent, Dr. Phipps directly address this passage in his Declaration wherein he stated:

> This statement requires no unique knowledge of drug transport and is an entirely obvious concept. That is, since drug flux was known to be independent of drug concentration over some concentration in a range (e.g., as stated in the Padmanabhan article), and since drug flux is obviously zero at zero concentration, then to conclude in the '894 patent that a "threshold value" exists is an obvious concept requiring no unique knowledge about the mechanism of drug transport through the tissue. In addition, the statement in the '894 patent that this threshold value is likely dependent on the fiscal/chemical properties of the drug species and tissues is also an obvious general principal that is the void of mechanistic or drug-specific knowledge.

What applicant has found that despite the evidence in the art that the threshold level is very low (down to 1 mM for hydromorphone) and despite the caveats in the art which warn about the potential misuse of narcotics in the electrodes thus counseling away from high concentrations, fentanyl requires a high concentration in order to maintain a relatively constant iontophoretic flux. Against all the background which would lead away from this conclusion, applicant's finding is not suggested by the art and is clearly patentable thereover.

The Examiner has yet further relied on Mueller et al. and selected isolated statements in this patent in order to justify the conclusion the Examiner has already reached. Mueller et al. does not relate to the iontophoretic delivery of fentanyl and certainly does not recognize the challenges which this specific drug presents. To take the position, as the Examiner apparently has on page 10 of the Action that it would be obvious

to design a device which contains ten times as much fentanyl in the donor reservoir as is to be administered, would be an invitation to potential abuse. Thus, Mueller et al. also would not lead to the specific invention defined in the claims of record.

The next rejection, based on Haak et al., U.S. Patent No. 5,203,768, either alone for anticipation purposes or in combination with Rebinder, the '894 patent and Mueller et al. or in view of Newman, U.S. Patent No. 4,931,046, is also believed to be improper. Haak et al. describes a transdermal drug delivery device which includes both an active drug reservoir (from which drug is delivered by iontophoresis) and a passive drug reservoir (from which drug is delivered by diffusion). In the example provided by the patent, fentanyl is delivered in an amount of 25 μg/hr. by passive delivery and a bolus of 25 μg every 5 minutes can be delivered by iontophoresis for a total delivery rate of 325 μg/hr. The Examiner has interpreted this single statement as indicating that the device must act in a linear fashion for the patentee to make this statement so that it is inherent that the concentration is in a range defined in the claims of record.

The Examiner has misinterpreted the teachings of Haak et al. The delivery rate of 325 μg/hr. is solely based on a calculation of the base delivery rate from the passive drug reservoir in addition to that provided by the active drug reservoir. There is absolutely nothing in the patent which leads to the understanding that the total delivery period should be terminated while the claimed concentration of fentanyl still resides in the donor reservoir. Quite to the contrary, it would be entirely consistent with the teachings of Haak et al. to operate the device until the active electrode reservoir is completely emptied of the

drug. Since the result hypothesized by the Examiner is not a necessary result, as opposed to merely a possible one, it is evident that an anticipation rejection cannot properly exist.[3]

The additional documents relied on in the remainder of the rejection would also not result in the presently claimed invention. While Haak et al. does describe the iontophoretic delivery of fentanyl, (*albeit* in combination with passive drug delivery), one would still not arrive at the realization that the total delivery period must be terminated while the level of fentanyl salt in the donor reservoir is above about 16 mM. Indeed, one would expect from the fair teachings of the art that one could operate the iontophoretic portion of the device until the donor reservoir was essentially empty and still maintain a linear correlation between current and flux. This is evident from the statement provided at column 10, lines 53-57 which states:

> For example, it may be desirable to deliver a predetermined constant level of current from device 10 since a constant current level ensures that the active agent is delivered through the skin at a constant rate.

There is absolutely nothing within Haak et al. which would lead those of ordinary skill in the art to terminate administration while the substantial amount of fentanyl is still present in the donor reservoir. In fact, in light of the aforementioned discussion regarding the article by Padmanabhan and the results set forth in the '894 patent which shows a steady state of delivery for hydromorphone hydrochloride at 10 mM, one would be led to believe that one could fully deplete the donor reservoir of fentanyl in Haak et al.

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[3] See Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746 (Fed. Cir. 1991).

The further reliance on Newman, U.S. Patent No. 4,931,046, illustrates a clear tempt to misinterpret the teachings set forth in the art in an effort to meet the recitations set forth in the claims of record. The Examiner has specifically referred to the passage starting at column 7, line 46 which indicates that the application of pain killing drugs in the disclosed iontophoresis drug delivery system can be monitored and controlled by monitoring the patient's heartbeat and that a microprocessor can be used to permit the patient to self-administer medication and to require intervening non-administration periods between doses of the drugs.

Even if one were to combine the teachings of Newman with those of Haak et al., one would still not arrive at the presently claimed invention. The teachings of Newman would lead to a device wherein the rate of administration of the drug is controlled. There is nothing in the patent which would lead to a system wherein the total drug delivery permitted by the system is terminated while a substantial amount of the drug, particularly a potent drug such a fentanyl, remains in the donor reservoir. Furthermore, there is nothing in Newman which in any way reflects an understanding as to why this defined concentration is used. Hence, the combination of Haak et al. with any or all of the other documents set forth in paragraph 4 of the Official Action would not lead those of ordinary skill in the art to the presently claimed invention.

The last prior art rejection based on Theeuwes et al. alone or in view of the other previously cited prior art. The Examiner's reliance on this patent is based on the claims which relate to an iontophoretic agent delivery electrode assembly which includes a drug

reservoir that contains an analgesic drug selected from the group consisting of fentanyl, sufentanil, analogs of fentanyl, analogs of sufentanil and pharmaceutically acceptable salts thereof. At the bottom of page 13 of the Action, the Examiner has admitted that the patent provides little information for such a method and device, but still takes the position that the invention is inherent from the claims.

The Examiner's reliance on the claims of Theeuwes et al. calls to mind the decision in In re Benno, 226 USPQ 683 (Fed. Cir. 1985). In that decision, the PTO had relied on the claims of a prior patent in order to reject the claims on appeal. Quickly reversing the rejection, the Court noted that the prior patent to Danti did not even hint at the problem sought to be solved and did not disclose what was defined in the claims on appeal. In discussing the difference between the claims and disclosure of a prior patent, the Court stated at pages 686-687:

> The scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses. A patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding. While it is true, as the Solicitor suggested at oral argument, that "a claim is part of the disclosure," that point is of significance principally in the situation where a patent application as filed contains a claim which specifically discloses something not disclosed in the descriptive part of the specification (claims being technically part of the "specification," 35 U.S.C. § 112, 2d par.), in which case the applicant may amend the specification without being charged with adding "new matter," within the meaning of § 132. ... But that is not the situation here. Danti's claim 1 does not disclose any structure additional to what the Danti specification discloses.

As admitted by the Examiner, Theeuwes et al. does not disclose the method and device defined in the claims of record. Thus, the Examiner cannot rely on the nature of the claims of the patent in order to justify a rejection of the claims of record. Furthermore, since the very basis for the Examiner's reliance is flawed, it follows that the additional reliance on the aforementioned Rebinder, '894 patent Mueller et al. and Newman also would not result in a recognition of what applicant has invented and has defined in the claims of record.

In addition to the prior art rejections set forth in the Action, the Examiner has now raised "obviousness-type" double patenting rejections over certain prior patents. More particularly, the Examiner has rejected method claims 1, 4 and 7-9 over claims 1-9 of U.S. Patent No. 6,171,294, and device claims 10, 13, 16 and 17 over claims 1-9 of U.S. Patent No. 6,216,033, both of which were examined by the Examiner in charge of the present application.

As set forth in Ex parte Oetiker, 23 USPQ2d 1651 (Bd. Pat. App. Inter. 1990), *affirmed*, 23 USPQ2d 1661 (Fed. Cir. 1991) (unpub), the test for obviousness-type double patenting is not whether the claims in one case are broader than in another, but whether the claimed invention in the subject application would have been obvious from the subject matter of the claims in the other case in light of the prior art. In making this determination, it is important to keep in mind that one cannot use the specification of the prior patent or application as "prior art", In re Kaplan, 229 USPQ 678 (Fed. Cir. 1986).

Applying the foregoing standards to the present circumstances, it will be appreciated that the '294 patent claims a method of obtaining self-administered analgesia by defining the dosage of fentanyl, the delivery period and the total number of additional doses over a period of 24 hours. The claims of the '294 patent do not lead to any understanding that when the final additional dose is applied, the concentration of fentanyl salt remaining in the donor reservoir must be above about 16 mM. In fact, it is entirely within the scope of the claims of the '294 patent that the final fentanyl dose could be withdrawn from a donor reservoir which contains a fentanyl salt concentration well below 16 mM. Indeed, there is absolutely nothing in the claims of the '294 patent which indicates any residual level of fentanyl in the donor reservoir. Thus, one would simply not arrive at the presently claimed invention defined by claims 1, 4 and 7-9 from claims 1-9 of the '294 patent and it follows that these claims of the present application are patentable over the claims of the '294 patent.

A similar analysis exist with respect to the '033 patent which defines in claims 1-9 a patient-worn device for transdermally delivering fentanyl by electrotransport and which comprises a donor reservoir hydrogel formulation comprised of fentanyl in a form to be delivered solely by electrotransport, a counter reservoir, a source of electrical power electrically connected to the reservoirs and a control circuit for controlling electrotransport current so that a defined dose of fentanyl over a defined delivery period is provided with from about 10 to about 100 additional doses permitted over a period of 24 hours.

Once again, there is nothing in the claims of the '033 patent to design the device so that the concentration of fentanyl salt is above about 16 mM throughout the total delivery period including the last additional dose. In this respect, while the claims of the noted patents may overlap that which is claimed in the present application, that fact in and of itself is not sufficient to support an "obviousness-type" double patenting rejection. Indeed, in the aforementioned Kaplan decision the Federal Circuit reversed an obviousness-type double patenting rejection where the claims of the earlier patent completely encompassed the claims of the application on appeal. Thus, the stated double patenting rejection cannot stand.

While applicant believes that the foregoing discussion rebuts the points raised by the Examiner's Response to Arguments set forth in the Action, such as by providing a specific reference which shows the potential dangers of abuse of narcotic drugs in an electrode of a electrotransport device and the absence of an effect of extraneous or competing ions in the present invention, some additional discussion is believed to be in order. More specifically, in the passage beginning at the bottom of page 17 of the Action, the Examiner has apparently misinterpreted applicant's claims and/or arguments. The claims recite that the level of fentanyl is above about 16 mM substantially throughout the total analgesic drug iontophoretic delivery period wherein the analgesic drug is delivered through the body surface. Based on the understanding provided in the specification and Example 1 and Figure 2, it is apparent that this recitation is of particular significance with regard to the concentration of fentanyl when the last administration of fentanyl from the device is

completed. In this respect, the starting concentration of the reservoir is a function of various factors including the size of the reservoir and the length of the designed period of administration and for this reason, one need not require a specific starting concentration. What applicant has maintained is that whatever starting concentration is used with fentanyl (but which of course is higher than about 16 mM), one would logically design the device to deplete the reservoir as completely as possible when the total delivery is completed given the possible abuse of this potent drug. In this respect, the Yerasi and Edinboro publications, which relate to fentanyl delivery by passive systems, were not meant to be representative of the present invention, but simply to meet the Examiner's statement on page 9 of the Official Action dated April 2, 1998, that "Notwithstanding, neither applicant nor the prior art demonstrate if overdosing is even possible using the salt forms of fentanyl and sufentanil by passive transdermal application much less concentrations and amounts approaching dangerous levels."

Not answered fentanyl

The documents referred to in the Action actually support applicant's position that those skilled in the art would avoid having residual drug in the reservoir. This is apparent from the aforementioned discussion in Petelenz et al. at column 16, lines 52-55 wherein cream or gel in an iontophoresis system is described which "minimizes the possibility of the drug being improperly extracted from electrode and misused."

A further patent cited by the Examiner, namely Gale et al., U.S. Patent No. 4,588,580, also reinforces applicant's position. In the passage beginning at column 1, line 47, the patent discusses the potential dangers of fentanyl and specifically states:

> Fentanyl and its derivatives are highly potent, rapidly metabolized drugs having a relatively narrow therapeutic index which produce extremely undesirable side effects on overdosage, most notably respiratory depression, which if left unchecked can cause death. They are also relatively expensive and have a high potential for abuse. We have found that these characteristics impose numerous and sometimes conflicting design constraints on a practical transdermal delivery device. For example, **it would be desirable that the device deliver the drug at a substantially constant rate for at least about 24 hours while at the same time keeping the amount of drug within both the unused and depleted systems to a minimum.** (Emphasis added)

To the extent that the Examiner has quoted from Gale et al. (on page 18 of the Action and quoted from a different literature reference on page 19), it is apparent that the Examiner has drawn an incorrect conclusion. Such passages do not teach that fentanyl salts are not readily diffusible through the skin and do not create a potential danger. Rather, both refer to only fentanyl **citrate** and not fentanyl salts in general. For instance, the complete passage from which the Examiner has quoted states:

> We have found that there is a relatively wide range of permeability of normal human skin to fentanyl and this permeability not only varies from individual to individual and site to site but is also highly dependent on the chemical form of the drug. We have discovered that fentanyl citrate, the form in which fentanyl is presently administered, has such a low skin permeability that it is not at all suitable for transdermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base.

Thus, the art is well aware of the potential dangers of fentanyl and cautions against residual drug in the reservoir which has the potential of being misused.

As to the Examiner's apparent questioning of the sufficiency of disclosure, applicant has provided a clear teaching that the defined concentration of fentanyl salt is to

be maintained throughout the delivery period in order to maintain substantially constant flux. It is well within the skill of the art to design a control circuit by which this can be attained. For instance, it has been noted at the bottom of page 3 of the specification that control circuits can be designed to control the amplitude, polarity, timing, waveform, etc. of the electric current and/or voltage. Additional discussion of the circuitry can be found on pages 22 and 23 and in Example 3 a device is described which limits the total number of doses. Thus, those of ordinary skill in the art would have absolutely no problem in providing a system wherein the administration of the fentanyl is completely terminated while the concentration of the drug in the donor reservoir is above the defined limit.[4]

For all of the reasons set forth above, applicant respectfully submits that the claims of record are neither anticipated nor rendered obvious by the individual documents or extensive combinations set forth in the Official Action. Applicant further maintains that the Examiner's "obviousness-type" double patenting rejections are improper. Thus, reconsideration and allowance of the present application are respectfully requested.[5]

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[4] As noted in MPEP §2164.05(a) and the cases cited therein, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled in the art and already available to the public.

[5] While applicant has attempted to address each point raised in the extensive Action, it should not be construed as a concession if applicant has inadvertently failed to address one or more points raised therein.

Should the Examiner wish to discuss any aspect of the application, he is invited to contact the undersigned attorney at the number provided below.

Respectfully submitted,

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Attachment to Amendment dated February 26, 2002

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Page 24, Paragraph Beginning at Line 23

The transdermal electrotransport fentanyl flux from these gels was measured by *in vitro* flux studies using a two-compartment diffusion cell and human cadaver skin. The gels were mounted on the stratum corneum side of heat stripped human cadaver epidermis taken from back skin samples. The other side of the epidermis was exposed to a receptor compartment, having a volume of 4 [cm^2] cm^3, and filled with one tenth strength Dulbecco's phosphate buffered saline (pH 7.4). A counter electrode comprised of a polyisobutylene film loaded with silver chloride powder was placed in the receptor compartment.